human serum may be used to stimulate the immune system in patients. Based upon these references, it is concluded that DPP IV actually acts to promote an immune response and therefore it would have exactly the opposite effect that would be desirable in the treatment of conditions such as rheumatoid arthritis.

Applicants respectfully traverse this rejection.

It is well established in the art that substance P is a neurotransmitter involved in transmitting pain signals in conditions such as arthritis. The Examiner appears to accept Applicants' assertion that DPP IV is effective in degrading substance P. Thus, absent evidence to the contrary, it is reasonable to conclude that, by interfering with pain signal transmission, DPP IV should reduce the pain associated with arthritis and be a useful treatment for this condition. The Examiner has cited several references which allegedly provide evidence that DPP IV would *not* be an acceptable therapy for arthritis patients despite its action against substance P. However, Applicants do not believe that this conclusion is justified.

The role of DPP IV in the immune response is discussed in the Duke-Cohan reference cited by the Examiner (see Background and Summary of the Invention sections). This makes it clear that there are at least two different types of enzymes present in individuals which have DPP IV activity. There is a 105 kDa form (referred to therein as CD26) which is found on the surface of T cells, but only in very small amounts in human serum. It is this membrane-bound form of the enzyme that is referred to by Applicants in the present application (see page 5 of the application, lines 9 and 10, citing Misumi, *et al.*, *Biochim. Biophys. Acta* 15:1131 (1992)).[1] This enzyme promotes the proliferation of T cells in response to the presence of recall antigen (see Duke-Cohan, col. 1, lines 38-61). Stimulation of T cell proliferation also occurs when the enzyme is added extracellularly and such proliferation would clearly be undesireable in the treatment of arthritis. However, it is important to note that there is *no* effect on proliferation in the absence of recall antigen (see col. 1 of Duke-Cohan, lines 55-58). Arthritis, particularly rheumatoid arthritis, is generally accepted to be an autoimmune

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[1] The reference is entitled, "Molecular Cloning and Sequence Analysis of Human Dipeptidyl Peptidase IV, a Serine Proteinase on the Cell Surface," and was submitted by Applicants in connection with an Information Disclosure Statement as reference AM4. See also references by Abbott, *et al.* (cited as references AL1 and AM1) and Darmoul, *et al.* (cited as reference AP1).

disease in which a person's immune system attacks the body's own healthy tissue. It represents an abnormal activation of the immune system and is not a response that is associated with a recall antigen. Thus, the Duke-Cohan reference does not suggest that the membrane type DPP IV would cause a proliferation of T cells in an arthritic individual.

There is a second type of enzyme with DPP IV activity that is referred to in the Duke-Cohan reference, a serum form that is 175 kDa and which is actually the subject of the claims in that patent. Although this form appears to have a similar enzymatic activity as the membrane-bound form, it responds differently to at least one inhibitor and is structurally distinct. The patent indicates that the 175 kDa enzyme is the predominant form in serum and is not a breakdown product or caused by the shedding of the membrane-bound DPP IV from cells (see, *e.g.*, col. 5 of Duke-Cohan, lines 1-5 and 63-64). The serum enzyme does stimulate T cell proliferation, but, again, it is reported to do so *only* in the presence of recall antigen, *e.g.*, tetanus toxoid (see Example VII, col. 11, lines 41-58). There is no indication or suggestion that the enzyme would stimulate the proliferation of cells in an arthritic patient. Applicants therefore submit that the Examiner's reliance upon this reference as presenting teachings that DPP IV would exacerbate arthritis is unwarranted.

The other references cited by the Examiner allegedly teach that inhibitors of DPP IV are effective in treating arthritis. The apparent implication arrived at by the Examiner is that adding additional intracellular DPP IV would therefore have the opposite effect, *i.e.*, it would make arthritis worse. Again, Applicants do not agree with this conclusion. As discussed above, there is a membrane-bound, 105 kDa, form of DPP IV which is present in very small amounts in serum and a 175 kDa enzyme that is present in serum in a much higher amount. The Tanaka and Villhauer references do not recognize different enzymatic forms, but since these references were written before the Duke-Cohan reference was published, it seems most likely that the inhibitors referred to are active against the membrane form of the enzyme.[2] It is also reasonable to conclude that the inhibitors examined in the references act by binding to this enzyme, preventing it from cleaving its normal substrate, and thereby reducing the stimulus for T cell proliferation. Contrary to the Examiner's

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[2] Since, as mentioned previously, the 105 kDa form of DPP IV is reported by Duke-Cohan to be unaffected by one inhibitor effective against the membrane-bound form of the enzyme, it cannot be assumed that the inhibitors described in the Tanaka and Villhauer references would be effective against both forms of the enzyme.

conclusion, adding extracellular 175 kDa DPP IV would be expected to have the same effect. Specifically, the enzyme introduced into a patient's bloodstream should compete with the enzyme bound to the membranes of T cells for substrate. In effect, the added exogenous enzyme acts as an inhibitor of the membrane-bound enzyme. There is nothing in the references to suggest that the added enzyme would not carry out its known activity of cleaving substance P and thereby reduce the amount of pain experienced by the patient. The results presented in the references actually suggest that the added DPP IV might also work at another level to benefit arthritis patients even more.

Conclusion

In light of the discussion above, Applicants submit that the Examiner's rejections have been overcome. It is therefore respectfully requested that these rejections be withdrawn and that the claims presently pending in the application be allowed.

If, in the opinion of the Examiner, a phone call may help to expedite the prosecution of this application, the Examiner is invited to call Applicants' undersigned attorney at (202) 419-7013.

Respectfully submitted,

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